16 10. (Amended) The method according to claim 4 [any of claims 3 or 4] wherein said non-steroidal anti-inflammatory agent is selected from the group consisting of salicylate, phenylbutazone, indomethacin, acetominophen, phenacetin, naproxen and ibuprofen.

Please add new claim 13 as follows:

17 13. (New) The method of claim 1 or 2, wherein said amylin or amylin agonist is amylin.

Please cancel claims 3, 11 and 12 without prejudice.

In the specification:

At page 25, 1line 18, after "Application", please insert --Serial no. 60/231,182--.

REMARKS

This Response is timely filed as it is filed with a petition for an Extension of time and the appropriate fees, extending the time for response to May 17, 1999. Claims 1, 2, 4-8 and 10 have been amended. New claim 13 was added. Claims 3, 11 and 12 have been cancelled without prejudice. Applicants reserve the right to pursue this subject matter in this or any other appropriate patent application. The cancellation of this claim makes no admission regarding the patentability of this subject matter and should not be so construed. The application has been amended to correct various formalities noted by the Examiner. These amendments add no new matter, are supported by the application as filed and should not be construed as limiting the appropriate scope of protection provided by 35 U.S.C. 271 and the doctrine of equivalents. In

particular, the amendments to claims 1 and 2 are introduced to exclude the particular amylin agonist CGRP, which is discussed, for example at page 7, line 15. The amendment to claim 4 is supported throughout, for example, see the original claims and page 11, line 17 to page 13, line 4. The other amendments correct claim dependency or insert sequence identification numbers, or serial numbers, otherwise included or referenced in the original application.

Applicants explain in detail below why the Notice of Abandonment is improper and should be withdrawn and respond in detail to each of the issues raised by the Examiner in Office Action mailed November 17, 1998.

I. REQUEST FOR WITHDRAWAL OF NOTICE OF ABANDONMENT

Applicants respectfully request that the Examiner withdraw the Notice of Abandonment mailed March 4, 1999. The Notice of Abandonment states that the application is abandoned in view of Applicants' failure to timely file a proper response to the Office Action mailed on June 9, 1998. However, Applicants did, in fact, file a timely Response to the Office Action on September 2, 1998. In reply to Applicants' response, the Examiner mailed an Office Action on November 17, 1998, setting a month or thirty day period for response and stating that "EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 C.F.R. § 1.136(a)." Thus, with the enclosed petition for extension of time, the time period for filing a response is May 17, 1999 and the present response is timely filed.

Despite the above, the Examiner mailed a Notice of Abandonment on March 4, 1999 which did not consider the Response filed September 2, 1998 or the Office Action mailed November 17, 1998 which re-set the period for response. Applicants note that, while the November 17, 1998 Office Action stated that the Response filed September 2, 1998 was deemed non-responsive, it also stated that the September 2, 1998 Response appeared to be *bona fide* and re-set the period for response. After receiving a notice that they had an extended time (one month or thirty days plus extensions) to file a reply, Applicants were thus surprised to receive a notice of abandonment for failing to file a response before the extended time period had expired. The error of sending a Notice of Abandonment can clearly be seen from the following summary of the chronology of events:

6-9-98	First Office Action mailed
9-2-98	Response to First Office Action mailed
11-17-98	Second Office Action mailed (states Response is deemed non-responsive, that applicants are given one month or thirty days to respond, and that extensions of time are available, thus permitting until 5-17-99 to file a timely reply)
3-14-99	Notice of Abandonment (states application abandoned for failure to file timely response to 6-9-98 office action)
5-17-99	Response to Second Office Action filed with petition for extension of time

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the Notice of Abandonment mailed March 4, 1999.

II. CONDITIONAL PETITION FOR REVIVAL

If the above request to withdraw the March 4, 1999 Notice of Abandonment is not granted, then Applicants hereby petition to the Assistant Commissioner for Patents to revive the above-captioned application pursuant to §1.137(b) on the ground that the delay in providing a complete response was unintentional. Applicants are presenting this petition only in the event that the above request to withdraw the Notice of Abandonment is denied. Thus, if the request to withdraw the Notice of Abandonment is granted, then please ignore this petition and authorization to pay petition fees, as well as the enclosed terminal disclaimer

The above-captioned application was deemed to be abandoned for failure to provide a proper timely response to the Office Action mailed June 9, 1998.

Applicants' attorney declares that:

(1) the entire delay in submission of a proper timely reply for the above-captioned application, and thus the abandonment of the above-captioned application, was unintentional.

(2) Applicants are hereby petitioning the Commissioner to revive the above-captioned application under 37 C.F.R. §1.137(b). Pursuant to 37 C.F.R. §1.137(b) and MPEP 711.03(c), in order to revive an abandoned application, the petition must be accompanied by (1) a proposed response; (2) a petition fee; (3) a statement that the entire delay was unintentional, and a terminal disclaimer. To this end, Applicants enclose: (1) the present paper which constitutes a proper timely response to the June 9, 1998 Office Action, (2) the fee required for revival of an

unintentionally abandoned application pursuant to 37 C.F.R. §1.17(m), (3) a statement that the delay was unintentional, (4) a terminal disclaimer disclaiming the terminal part the statutory term of any patent granted on the instant application equivalent to the period of abandonment of the application. This disclaimer runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

Thus, Applicants respectfully request that this case be revived.

Kindly charge the fee under 37 C.F.R. § 1.17(m) in the amount of $660.00 (Small Entity) to Deposit Account 12-2475. If this fee is incorrect, or if any additional fees are due, please charge Deposit Account No. 12-2475.

III. THE OBJECTION TO THE DISCLOSURE

The disclosure stands objected to due to an allegedly incomplete reference to a provisional application and an allegedly improper incorporation by reference.

In order to advance prosecution and advance the case towards issuance, Applicants have amended the application to include the serial number of the referenced provisional application.

With respect to the incorporation by reference issue, Applicants respectfully submit that the Examiner has failed to explain why the material incorporated by reference is essential or to identify the portions of the applications incorporated by reference which are deemed essential. In addition, Applicants believe that the issue relating to citation of peptides by name or designation

other than by primary peptide sequence is now moot in view of the amendments to the application.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

IV. THE SEQUENCE RULES OBJECTION

The Examiner states that Applicants must insert the sequence identifiers with respect to the appropriate claims (*e.g.,* claim 7) in order to be in full compliance with the sequence rules.

In order to advance prosecution and advance issuance, Applicants have inserted sequence identifier(s) in the appropriate claim(s), as suggested by the Examiner. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

V. THE SECTION 102(a) AND 103(a) REJECTIONS OVER LIU ET AL.

Claims 1, 2 and 5 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by WPIDS Abstract No. 98-019088 to Liu *et al.*. In addition, claims 1, 2, 5 and 6 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liu *et al.*

In order to anticipate or render obvious a claimed invention, a reference must teach or suggest every limitation of claim. Claims 1 and 2 of the subject application relate to methods of treating or preventing gastritis or gastric ulceration by administering a therapeutically effective amount of an amylin or non-calcitonin amylin agonist; claims 5 and 6 depend from claims 1 and 2. The Liu *et al.* abstract –which relates to "Chinese medicines"- does not have anything to do with the peptide hormone "amylin." It states:

> Chinese patent medicine for curing gastrosis e.g. atrophic **gastritis**, surficial **gastritis** and gastric ulcer with 90% total effective rate, 50% cure rate and no toxic side effects is prepared from 13 Chinese-medicinal materials e.g. astragalus root and white peony root by proportioning, breaking, decocting, concentrating, purifying, concentrating again, mixing with cane sugar and **amylin**, granulating, drying and packaging.

Applicant respectfully submits that the Examiner has failed to show that the Liu *et al.* abstract anticipates the presently claimed invention. It is clear that the compound referred to by the Liu *et al.* abstract, which relates to the mixture of 13 Chinese herbs with fillers, such as sugar, is not the peptide described in the present application as "amylin". Amylin is not a "Chinese medicine". The Liu *et al.* abstract may refer, for example, to a plant extract that has been referred to in the past as "amylin" by workers in some of the former Eastern Bloc countries but that is not the compound amylin described in the present application. Thus, Applicant respectfully submits that the Patent Office has failed to meet its burden and has failed to demonstrate that the "amylin" of the Liu *et al.* reference is, in fact, the compound referred to as amylin in the present application.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

VI. THE REJECTION BASED ON KOLTERMAN

Claims 1-2 and 5-8 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Kolterman *et al.*

In order to anticipate or render obvious a claimed invention, a reference must teach or suggest every limitation of claim. The rejected claims generally relate to the treatment or prevention of gastritis or gastric ulceration with amylin or a non-calcitonin/non-CGRP amylin agonist. The Kolterman *et al.* PCT publication is said to describe the use of amylin or amylin agonists to reduce gastric mobility and slow gastric emptying. The Examiner argues that use of the same peptide(s) in the same way and in the same amount would necessarily or inherently anticipate the presently claimed invention. That amylin agonists reduce gastric motility and slow gastric emptying at certain doses and modes of administration, as defined and disclosed in the Kolterman *et al.* PCT publication, does not render obvious within the meaning of section 103 the gastroprotective effects of amylin and the use of the claimed compounds to treat gastritis or gastric ulceration.

Indeed, the gastric slowing and gastroprotective actions of a number of peptides can be clearly dissociated. For example, the most potent known inhibitor of gastric emptying known (exendin-4) has no apparent effect on gastric acid secretion. See Gedulin, B.R.//Lawler, R.L.//Jodka, C.M.//Young, A.A. "Comparison of effects of amylin, glucagon-like peptide-1 and exendin-4 to inhibit pentagastrin-stimulated gastric acid secretion." Diabetologia 40 (Suppl 1):A300, 1997. Thus, the Kolterman *et al.* application has no predictive value regarding the gastroprotective effects of amylin agonists. Applicants respectfully submit that the Examiner has failed to show that the subjects described in Kolterman *et al.* had or were susceptible to gastritis

or gastric ulceration or that the Kolterman *et al.* PCT publication would suggest administering amylin or a non-calcitonin amylin agonist to such a patient.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

VII. THE SECTION 103 REJECTION OF CLAIMS 1-3, 5-6, 11 AND 12

Claims 1-3, 5-6, 11 and 12 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans *et al.*, Gray *et al.*, Maggi *et al.*, and Gheczy *et al.*

In order to render obvious a claimed invention, the cited references must suggest every limitation of the claimed invention. Here, the rejected claims generally relate to methods of treating or preventing gastritis, gastric ulceration, or conditions which indicate use of a non-steroidal anti-inflammatory agent with an amylin or non-calcitonin amylin agonist and to related pharmaceutical compositions.

The Examiner concluded that:

> Accordingly, it would have been obvious at the time of Applicant's invention to utilize an amylin agonist (e.g. CGRP) alone to alleviate stomach inflammation (e.g. gastritis, ulcers etc.) or concomitantly (e.g. in combined pharmaceuticals or in separate administrations) with NSAID's in order to alleviate the undesirable side effects of NSAIDS (e.g. stomach inflammation and/or ulcers), as disclosed in the above references, with a reasonable expectation of success.

This statement appears to presuppose that gastroprotective actions in general will benefit ulcerogenic conditions in general. This is not necessarily the case. Guidobono *et al.* (Br. J.

Pharmacol. 125(1):23-28, 1998) recently reported "that the mechanisms involved in the anti-ulcer effects of amylin are different in [these two] different types of gastric lesions, probably because of the different etiopathology of various types of ulcers," indicating that generalizations of this sort cannot be made. Nonetheless, in order to expedite prosecution and advance the case towards issuance, Applicants have amended claims 1 to specifically recite that the amylin agonist is not a CGRP (claims 2, 5, and 6 depend from or ultimately depend from these claims and claims 3, 11 and 12 have been cancelled without prejudice). Thus, this issue is now moot.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

VIII. THE SECTION 103 REJECTION OF CLAIMS 1-3 AND 5-12

Claims 1-3 and 5-12 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Evans *et al.*, Gray *et al.*, Maggi *et al.* and Bates *et al.* in view of the present specification, Kolterman and Liu *et al.*, taken separately or in combination.

As noted above, in order to render obvious a claimed invention, every limitation of the claims must be suggested by the cited references. Also as noted above, the rejected claims generally relate to methods of treating or preventing gastritis, gastric ulceration, or conditions which indicate use of a non-steroidal anti-inflammatory agent with an amylin or non-calcitonin amylin agonist and to related pharmaceutical compositions.

The Examiner concluded:

> Thus, the skilled artisan would have a reasonable expectation to expect that amylin and its analogues (e.g. tri-Pro amylin) would act similarly to amylin analogs (e.g. calcitonin and CGRP) which were shown in the primary references to possess gastric protective activity (e.g. anti-ulcer or anti-inflammatory activity). Accordingly, it would have been prima facie obvious to the skilled artisan at the time of applicant's invention to substitute amylin and its analogues for amylin agonist (e.g. CGRP and calcitonin) to obtain pharmaceuticals containing amylin or analogues thereof the their expected use in preventing/treating gastritis or ulceration alone or combined with NSAID's in order to alleviate the NSAID's known side effects (e.g. stomach inflammations, ulcers etc.) in view of the primary reference teaching of the amylin agonists use as antiulcer agents and the secondary references teachings of the functional equivalency of amylin agonists and amylin and its analogues in effecting gastric function.

Applicants respectfully submit that it is not obvious from the observation that calcitonin or CGRP is beneficial, that amylin agonists in general will also be beneficial. Blockade of the gastroprotective benefits of amylin with AC187, which blocks amylin receptors ~40-fold better than it blocks calcitonin receptors and blocks amylin receptors ~400-fold better than it blocks CGRPs receptors, indicates that it is primarily amylin agonism (rather than CGRP agonism or calcitonin agonism) that confers a beneficial gastroprotective action. E.g., Young, A.A.//Gedulin, B.R.//Gaeta, L.S.L.//Prickett, K.S.//Beaumont, K.//Larson, E.//Rink, T.R. "Selective amylin antagonist suppresses rise in plasma lactate after intravenous glucose in the rat." F.E.B.S. Letts, 237-241, 1997. Nonetheless, in order to expedite prosecution and advance the case towards issuance, Applicants have amended claim 1 to specifically recite that the amylin

agonist is not a CGRP (claims 2, and 5-10 depend from or ultimately depend from these claims and claims 3, 11 and 12has been cancelled without prejudice). Thus, this issue is now moot.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

IX. THE SECTION 103 AND DOUBLE PATENTING REJECTIONS OF CLAIMS 4-8 AND 10-12

Claims 4-8 and 10-12 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Young and Ghyczy *et al.* and under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-22 of Young *et al.* in view of Ghyczy *et al.*

As noted above, cited references must teach or suggest every limitation of a claimed invention in order to render the invention obvious. Here, the rejected claims generally relate to a method of enhancing the analgesic activity of a non-steroidal anti-inflammatory drug ("NSAID") by administering an amylin or non-calcitonin amylin agonist along with the NSAID.

The Examiner argues that:

> It would have been prima facie obvious to the skilled artisan at the time of applicant's invention to combine amylin or its agonists with NSAID's in order to effect "enhanced analgesia" with a reasonable expectation of success since the prior art recognized the separate analgesic utility of amylin and NSAID's which would motivate the skilled artisan to make combination pharmaceuticals thereof and in view of the express motivation presented in the '279 patent to do so.

In order to expedite prosecution and advance the case towards issuance, Applicants have amended claim 4 to depend from claim 1 or 2 and is thus patentable for the reasons discussed above (claims 5 and 6 depend from or ultimately depend from claim 4 and claims 11 and 12 have been cancelled without prejudice). Thus, this issue is now moot.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw these rejections.

CONCLUSION

Applicants believe that all claims are in condition for allowance and respectfully request early Notice thereof. Should any issues or questions remain, the Examiner is encouraged to telephone the undersigned so that they may be promptly resolved.

The Commissioner is hereby authorized to charge any additional fees that may be incurred or credit of any overpayment of fees to our Deposit Account No. 12-2475.

Respectfully submitted,

Date: May 17, 1999

By: _____

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